DETAILED ACTION

The Amendment filed 4/30/2008 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 35, 39-42, 44, and 50-51 have been amended.

Claims 60-70 have been added

Claims 6-34, 37-38, 43, 45-49, 52-54, and 56-58 have been canceled.

Remarks drawn to rejections of Office Action mailed 11/1/2007 include:

102 rejections: which have been overcome by applicant's amendments and have been withdrawn.

An action on the merits of claims 1-5, 35-36, 39-42, 44, 50-51, 55, and 59-70 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Election/Restrictions

It is noted, that upon further search and examination, an additional restriction requirement is being set forth herein.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1 in part, 2, 35-36, 39-41, 44 in part, 50-51, 55, 59 in part, 60, 66, and 67 drawn to methods of treatment with compounds of formula Ia, classified in class 514, subclass 49.

II. Claims 1 in part, 3, 42, 44 in part, 59 in part, 61, 68 drawn to methods of treatment with compounds of formula Ib, classified in class 514, subclass 45.

III. Claims 1 in part, 44 in part, , 59 in part, 62 in part, and 63 in part, drawn to methods of treatment with compounds of formula Ic, classified in class 514, subclass 45.

IV. Claims 1 in part, 4, 44 in part, 59 in part, 64, and 69, drawn to methods of treatment with compounds of formula IIa, classified in class 514, subclass 49.

V. Claims 1 in part, 5, 44 in part, 59 in part, 65, and 70, drawn to methods of treatment with compounds of formula IIb, classified in class 514, subclass 45.

VI. Claims 1 in part, 44 in part, 59 in part, 62 in part, and 63 in part, drawn to methods of treatment with compounds of formula IIc, classified in class 514, subclass 45.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-VI are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, one being treatment with compounds of formula Ia, one with formula Ib, one with formula Ic, etc. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to

petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

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Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Krista Bianco on 8/29/2008 a provisional election was made without traverse to prosecute the invention of Group I, claims 1 in part, 2, 35-36, 39-41, 44 in part, 50-51, 55, 59 in part, 60, 66, and 67. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3-5, 42, 61-65, and 68-70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 1 is objected to for containing non-elected subject matter. The subject matter of groups II-VI should be canceled from claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 66 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the viral infections, does not reasonably provide enablement for prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to a method of treating or preventing *Flaviviridae, Orthomyxoviridae,* or *Paramyxoviridae* viral infections, using the claimed nucleoside.

The state of the prior art

There are various known nucleoside derivatives which have efficacy in treating viral infections, as seen by Devos et al. (US 2004/0110718). At present, there are no known agents capable of preventing all *Flaviviridae, Orthomyxoviridae,* or *Paramyxoviridae* viral infections.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agent has efficacy in treating certain conditions associated with the claimed viral diseases, however the art is silent with regard to the predictability of effectively preventing the development of the viral infections by administering the claimed compounds.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written, i.e., nothing showing any preventative therapy. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are directed to the use of various compositions in testing their antiviral activity or ability to inhibit cell proliferation of various cell lines. There has not been provided sufficient evidence which would warrant the skilled artisan in virology or oncology, to accept the data and information provided in the working examples as correlative proof that a healthy individual would never become afflicted with any of the viral conditions or any cancerous condition if subjected to the instantly claimed therapy.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any of the compositions to prevent the development of the claimed viral diseases or cancer without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Reasonable guidance with respect to preventing any condition relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of the condition. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of the clinical condition and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment

and subsequent knowledge of the prevention of the disease is the essence of verification of a valid preventive agent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 provides that the nucleoside of formula I-a "is selected from one of the following", and then lists a table. However, it is noted that the table does not list all of the variables, i.e., D is not listed in the table. Since the preamble states the compound is selected from "one of the following", it is unclear what moiety (note singular) is intended to be D. Adding a column for D, or changing the preamble to read something like "wherein the nucleoside of formula Ia has variables for X^1, Y^1, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ selected from one of the following rows".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 41, 44, 60, and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Loeb et al. (WO98/18324).

Loeb et al. disclose methods of treating various viral infections, including HCV, flavivirus, influenza virus, measles, mumps, and RSV (see page 7, lines 23-35) with various modified nucleosides, such as with N4-aminocytidine, 5-hydroxycytidine (page 26, 1st full paragraph) and 5-hydroxyuridine (page 9, line 21).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 35, 36, 39-41, 44, 50-51, 55, 59-60, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loeb et al. as applied to claims 1, 2, 41, 44, 60, and 67 above, and further in view of Filippini et al. (Arch Virol (2000), 937-944 - of record) LaColla et al. (6,812,219 – of record) and Shealy et al. (J. Med Chem., 1986 (29) 1720-25 – of record from IDS filed 4/30/08).

The claims of the instant application are drawn to methods of treating various viral infections, such as from Flaviviridae, Orthomyxoviridae, or Paramyxoviridae infections using various nucleosides.

Loeb et al. teaches to treat various viral infections with modified nucleosides which induce a mutation in the virus wherein the increase in mutation rate results in a reduced viability of progeny generations of the virus. Various modified nucleosides administered include 5-hydroxycytidine and N4-aminocytidine, which are encompassed by the claims as set forth supra. What they do not teach is the additional various claimed compounds for treating the viral diseases.

Filippini teaches methods of treating HCV and HIV patients with various nucleosides such as zalcitibine, which is a 2',3'-dideoxynucleoside.

LaColla et al. disclose a multitude of modified nucleosides, including 2',3'-dideoxy nucleosides, for the treatment of flavivirus, and HCV infections. See column 143, line 18.

Shealy et al. teach that various 5-halocytosine compounds have analogous properties in inhibiting viral replication.

It would have been obvious to one of ordinary skill in the art to modify the various nucleosides of the prior art to treat various viral infections with these references before them. Obviousness based on similarity of structure and function entails motivation to make claimed compound in the expectation that compounds similar in structure will have similar properties. Where the prior art compounds essentially bracket the claimed compounds and are known to be effective as well known pesticides, for example, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new pesticides. See ***In re Payne, 606 F.2d 303, 203 USPQ 245, 254-55 (CCPA 1979).*** Moreover, it would be obvious to treat other members of Flaviviridae, Orthomyxoviridae, or Paramyxoviridae viral infections with the same drugs, as Loeb teaches that overlapping modified nucleosides can be used to treat all of the above classes of viral infections. As such, applicant's proviso at the end of claim 35, for example, is not seen to render patentable the claim, as the compound delimited would still be seen to be obvious to treat other flavivirus infections, for example, or treat the flu. Moreover, modifying zalcitibine with a 5-fluoro group on the base would also be obvious, as various 5-halogen cytidine compounds are taught to be effective in Loeb et al. (see cytidine compounds on page 26) and Shealy et al. The art teaches various divergent nucleoside derivatives are effective in treating the same groups of viral infections claimed in the instant application. As such, absent unexpected results, the methods of treating obvious viruses with obvious compounds is seen to be obvious in view of the references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRAVISS C. MCINTOSH III whose telephone number is (571)272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Traviss C McIntosh III/
Examiner, Art Unit 1623
August 28, 2008